REMARKS/ARGUMENTS

Affirmation of Election

Applicants hereby affirm the election of claims 1-11. This election is made with traverse, since the differences between the two groups of claims are not great enough to require a separate search or to place a significantly greater search or examination burden on the examiner than either one of the groups alone.

Support in the Application as Filed for the Amendments

Paragraph 0019: The sentence added to this paragraph is taken from claims 4 and 6 as originally filed.

Claim 18: The recitation of the establishment of a baseline range of nitric oxide concentration is supported in the specification at page 4, paragraph 0018. The recitation of samples taken at least 3 times per week is supported at pages 5-6, paragraph 0022 (lines 1-2 of page 6). The recitation of a deviation of 5 ppb as a limit based on an exhalation rate of 50 mL/sec is supported at page 6, paragraph 0024 (lines 22-25 of the page. The recitation of a decreasing trend as a factor in determining whether to modify a treatment protocol is supported at page 6, paragraph 0023 (lines 10 and 11 of the page). The recitation of waiting at least five days after a modification before making further modifications is supported at page 6, paragraph 0023 (lines 14-15 of the page).

Claim 19 is supported at page 6, paragraph 0024 (lines 20-21 of the page).

Claim 20 is supported at page 7, paragraph 0027 (lines 5-6).

Claim 21 is supported at page 7, paragraph 0023 (lines 12-14).

Claim 22 is supported at page 7, paragraph 0023 (lines 12-14).

Claim 23 is supported at page 14, claim 6.

Claim 24 is supported at page 14, claim 4.

Claim 25 is supported at page 5, paragraph 0019 (line 3 of the page).

Claim 26 is supported at page 4, paragraph 0017 (lines 19-21 of the page).

Claim 27 is supported at page 4, paragraph 0017 (lines 19-21 of the page).

No new matter is presented by any part of this amendment.

Objections to the Specification and Abstract

All such objections are removed by the above amendment.

Claim Rejections -- 35 USC § 112

The rejections under this section of the statute are likewise removed by the above amendment.

Claim Rejections -- 35 USC § 103

In view of the new claims, withdrawal of these rejections and reconsideration of the application is respectfully requested.

The present invention recognizes that the cause of asthma is pulmonary inflammation and that inflammation cannot be measured directly, only through its symptoms. The invention also recognizes that the symptoms of inflammation are also subject to constrictive events that are not related to inflammation. As a result, patients suffering from pulmonary inflammation can be asymptomatic due to factors that are not related to the inflammation. These factors include environmental conditions, the presence of other treatment administered simultaneously, and reactions to treatments and to changes in treatments. These factors can be transitory, and voluntary or involuntary, and different individuals will respond in different ways, depending on their individual immune systems and on their recent history of exposure or treatment. This obscures the reliability and value of individual measurements, and even successive measurements.

The innovation introduced by this invention is the use of repeated treatments taken over a period of time to determine a trend in the measured values, comparison of the trend with a baseline tailored to the individual, the baseline also having been determined by repeated measurements over time, the use of this comparison to decide whether a modification in the treatment is needed and what type of modification, and the type of monitoring to be performed subsequent to the modification to determine the effect of the modification and to decide whether further modification is needed. All of these parameters are recited in the new independent claim.

The resulting invention is distinct from modifications based on individual measurements and based on comparisons of individual measurements to a target value.

None of the references disclose or suggest a protocol defined in this manner.

Kharitonov et al. (*Monaldi Arch. Chest Dis.* 1996) refer to the use of exhaled NO for "monitoring" (p. 533, left col.) and for "assessing the anti-inflammatory effect of inhaled asthma treatments" (p. 535, right col.) and states that "absolute values are less important than serial measurement in individual patients" (p. 536, left col.). There is no discussion of a comparison of detected values with a baseline, of the particular results that should initiate a modification, and of how the modification should be monitored. Nor is there sufficient disclosure to enable the person skilled in the art to take measurements and process them in the manner presently claimed, noting again that the present claims recite parameters that are specifically directed to achieving control in any individual in any environment and with any aberration or special circumstance in the individual's recent physiological history. The value and advantage of Applicants' invention as now claimed can only be known through the act of discovery, not by routine experimentation with the disclosure of Kharitonov et al. as starting point. By simply referring to "monitoring" and "serial measurement," Kharitonov et al. do not lead one to such features as a minimum frequency of measurement and a minimum length of time to allow a treatment modification to affect the subject's condition before considering further modification to the treatment protocol. By their own admission, Kharitonov et al. rely on "precise" measurement (p. 536, left col.), which is a reference to individual measurements rather than to trends.

The downloaded website ("Information for transcriptionists ...") has been cited for its disclosure of the use of websites in general for uploading medical data. This is the only relevance of this reference. The website offers no recognition of the special needs of measurements of exhaled NO as an indication of pulmonary inflammation. There is no mention or suggestion of what one would compare to what, much less a comparison between a trend and a baseline, or how either would be obtained, or how one would modify a treatment protocol and then assess the effect of the modification, much less in the special ways needed for the control of pulmonary inflammation.

The Silkoff et al. patent is a disclosure of individual measurements of exhaled NO and their use as "an index of the response to therapy, or patient compliance in therapy" (column 2). The problem addressed by Silkoff et al. is "expiratory nasal contamination" (column 14, first paragraph under "Discussion") of exhaled pulmonary gas. This is a single-measurement problem, not a trend problem, and does not recognize the role that a baseline can play in a treatment protocol. There is no mention or suggestion of comparing a trend obtained over a period of time to a baseline, or of any particular way to modify a treatment protocol and then assess the effect of the modification, much less in the special ways needed for effective control of pulmonary inflammation in a manner suited to individuals and compensating for differences among individuals.

The Gaston et al. patent is strictly a disclosure of a device and its structure and use. There is nothing in Gaston et al. about a measurement protocol other than individual measurements. There is mention of multiple measurements, but these are only for purposes of calculating a "mean" and were not taken over a time period of days or weeks, but instead simply during the process of normal breathing. Like the references discussed above, Gaston et al. fail to mention or suggest any way of, or value in, comparing a trend obtained over a period of time to a baseline, or of any particular way to modify a treatment protocol and then assess the effect of the modification, much less in the particular ways set forth in Applicants' amended claims, which compensate for differences among individuals and provide effective control of pulmonary inflammation.

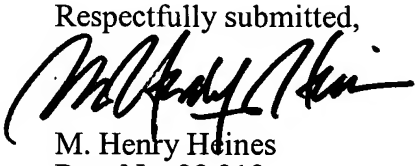
The Karitonov et al. paper in *The Lancet* states that "Because NO measurement is simple and non-invasive it can be repeated ..." (page 134, right column). This statement appears to be the most relevant to Applicants' invention as presently claimed. This statement of course lacks any guidelines, details, or suggestion of the detection of trends and the use of trends so detected for comparison to a baseline as a basis for changes to existing treatment protocols, or any particular way of monitoring measurements subsequent to the treatment change.

While the various references are discussed individually above, they each lack the basic components of Applicants' invention as presently claimed, which are the use of a baseline rather than a target value to detect a condition that needs attention, the development of a trend

over a specified period of time for use in the comparison with the baseline, and the importance of a specified monitoring protocol after any changes have been made to determine whether further changes are needed and of what magnitude and direction. For these reasons, Applicants respectfully submit that the invention as recited in these new claims is patentably distinct over the teachings of all of the cited references. On this basis, therefore, reconsideration of the application is respectfully requested.

Should any matters remain that might be resolved by a conference with Applicants' attorney, the examiner is encouraged to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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